Review of ACIP document: "Prevention of Rotavirus Gastroenteritis among Infants and Children: Recommendations of the Advisory Committee on Immunization Practices."

1. Clinical and epidemiologic features of rotavirus disease

   The clinical and epidemiologic features of rotavirus disease have been studied extensively and are thoroughly understood. The relevant results of clinical and epidemiologic studies are included in the statement.

   The document accurately describes the clinical and epidemiologic features of rotavirus disease and the impact of rotaviral infections on infants and children in the United States and worldwide.

   Rotavirus is the most important viral cause of diarrheal disease in infants and young children in the United States. Almost all children are infected with rotavirus by age 2 and most primary infections result in a symptomatic illness. Multiple serotypes produce disease and protection following the first infection is not complete. Subsequent infections are usually milder than the initial one. Rotavirus accounts for the majority of severe episodes of gastroenteritis in infants less than 3 years of age and each year, is responsible for a large number of visits to physician's offices and emergency rooms. Complications include dehydration and electrolyte imbalances leading to 55-70,000 hospitalizations and up to 70 deaths in the US each year. Nosocomial infections during rotavirus season are common. Well designed epidemiologic studies indicate that the burden of disease is similar across the United States has not changed in the past 25 years. In underdeveloped countries, rotavirus is the most common etiology of fatal episodes of gastroenteritis.

2. Rationale for rotavirus immunization

   The document accurately describes the rationale for rotavirus immunization; utilizing and accurately detailing available data on incidence, management and complications of rotavirus infection in the United States.

   The incidence of rotaviral infections in infants and young children is high in the United States. In spite of the availability of physicians and the use of both maintenance and rehydration fluids designed to manage infants with gastroenteritis and mild to moderate dehydration, severe episodes of rotavirus gastroenteritis continue to be associated with a large number of hospitalizations and 20-70 deaths in the United States annually. Worldwide, nearly 500,000 children die each year due to rotavirus infection and its complications. The initial rotavirus infection is usually the most severe. The immunologic response to the first infection offers enough protection to reduce the severity of subsequent rotaviral infections. Thus a vaccine would be beneficial if it offered enough protection against prevalent serotypes of rotavirus to reduce the severity and complications of the primary natural infection.

3. Morphology, antigen composition and immune response

The document adequately describes the morphology or rotavirus and the antigenic composition of currently circulating serotypes. The document also effectively discusses the current understanding of the immune response to rotavirus and the protection which results from infection and cites appropriate literature.

The morphology of rotaviruses is well described. They are 70-nm nonenveloped RNA viruses. Two structural proteins determine the serotype of rotavirus: VP4 (P protein) and VP7 (G protein). Rotaviruses are designated by their G serotype specificity. Six serotypes containing a variety of P and G combinations (P1AG1, P1BG2, P1AG3, P1AG4, P1AG9 and P2AG9) are prevalent in the United States.

The correlates of immunity are not fully known. It is thought that neutralizing antibody to the P and G proteins is responsible for protection. Studies have yielded conflicting results about the role of serum antibodies. The initial infection with rotavirus confers some protection against subsequent infections and those children who experience subsequent infections have milder symptoms than experienced with the first episode.

4. Bovine rotavirus-based pentavalent rotavirus vaccine (RotaTeq®)

The document provides a thorough review of the Phase III vaccine trials and the results which led to licensure of the bovine rotavirus-based pentavalent rotavirus vaccine.

The bovine rotavirus-based pentavalent rotavirus vaccine is a reassortant vaccine. Four of the reassortant viruses have the outer capsid proteins of the human G1, G2, G3, and G4 parent and the P7 attachment protein from the bovine parent strain. The fifth reassortant virus contains the P1A from the human rotavirus parent and the G6 from the bovine rotavirus parent.

This pentavalent vaccine was evaluated in a large placebo controlled trial which enrolled 72,324 infants (36,324 receiving vaccine and 35,825 receiving placebo). The vaccine proved to be immunogenic, resulting in an increase in group-specific IgA antibodies in 93-100% of vaccine recipients in the immunogenicity arm of the study. In the analyses available so far, no interference was noted with any of the routinely recommended vaccines for this age group of recipients. Studies on the response to acellular pertussis vaccine are not fully completed.

The vaccine proved to be highly efficacious in prevention of rotavirus gastroenteritis of any severity, and 98% effective in prevention of severe gastroenteritis. The vaccine reduced office visits, emergency room visits and hospitalizations. A high level of efficacy was also shown during the second rotavirus season after vaccination.

The vaccine proved to be safe with a serious adverse reaction rate of 2.45% vs. 2.6% for placebo recipients. Adverse experiences included vomiting, diarrhea, nasopharyngitis, otitis media and bronchospasm. Safety was also assessed in preterm infants.

A specific aim of the trial was to evaluate whether intussusception occurred after vaccine administration. Intussusception risk was evaluated in 71,725 subjects. An appropriate definition of intussusception was developed prior to the study and cases were evaluated by blinded adjudicators. There were as similar number of cases of intussusception in both groups and there was no evidence of clustering of cases within the first or second week after vaccine dose administration.

In summary, these were well designed trials which provided conclusive evidence that the bovine rotavirus-based pentavalent rotavirus vaccine was safe, well-tolerated, and highly effective in preventing severe rotaviral disease in young infants. The vaccine was also shown to have a significant impact on office and emergency room visits and on hospitalizations. In addition, the study was large enough to determine that there is no association with intussusception in this age group of recipients.

5. Cost-effectiveness analysis

The document accurately describes and summarizes available cost-effectiveness research.

Comprehensive cost-effectiveness analyses, utilizing available national data on the incidence of rotavirus infection, the number of visits required for care of affected infants and children and the number of hospitalizations resulting from complications, have enabled an accurate assessment of the effect of a recommendation for universal immunization. These analyses have indicated that universal immunization would result in a significantly reduced number of physician visits, emergency room visits, hospitalizations and deaths. The analyses also indicate that a universal rotavirus immunization program could be cost-saving or result in a net cost to society depending on the cost of the vaccine. The statement includes recent CDC data analysis which indicates that at a cost of $42 per dose, the vaccine would likely be cost saving, but at a cost of ~79$ per dose, it would be expected to result in a net cost.